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A. K. Takayama
Iowa State University

D. S. Busch

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Pemphigus: An Autoimmune Complex in Dogs and Cats

A. K. Takayama, BBA, BS, DVM*
D.S. Busch, DVM**

Introduction

The name Pemphigus, derived from the Greek word for blister, describes a group of vesiculobullous diseases of the skin of dogs, cats, and humans. The pemphigus complex is an autoimmune disease of the skin characterized by lesions ranging from vesiculobullous/pustular to erosive/ulcerative. Lesions of pemphigus are due to the binding of autoantibody to an antigen in the epidermal cell membrane or the glycocalyx causing a release of an enzyme(s) resulting in disruption of intercellular attachments and acantholysis.¹

Pemphigus produces lesions that are restricted to the epidermis. More specifically, these lesions are suprabasilar, each variant being characterized by location within the epidermal layer and by location of lesions on the body.

Pathogenesis

There are several mechanisms proposed for the breakdown or loss of control in self-tolerance. Gorman and Werner have proposed the following mechanisms of autoimmune disease: "(1) polyclonal B cell activation -- B cell clones are stimulated by a pathogen as well as autoreactive B cell clones resulting in the production of autoantibodies, (2) T suppressor cell bypass -- effective T cell suppression is bypassed when the presence of an exogenous agent on a cell surface induces a response to the exogenous antigen and the cell surface antigen, (3) T suppressor cell dysfunction-- allows expansion of autoreactive B cell and T cell clones, (4) increased T helper cell function-- increases recognition and induction of a re-

sponse to the host cell antigen by T helper cells, (5) autoantigen modification -- modification of a host cell antigen that renders it autoantigenic, (6) cross-reacting antigens -- sharing of determinants between exogenous antigens and host cell antigens."⁵ In addition to these, Muller et al proposes an inappropriate interleukin 2 production and an idiotypic-anti-idiotypic imbalance as well as sexual dimorphism ("with female sex hormones tending to accelerate immune responses and male sex hormones tending to suppress responses") as mechanisms of autoimmune diseases.² The pemphigus complex is a group of disorders characterized by an inappropriate immune response.

Although the exact mechanism of lesions produced in pemphigus is not fully understood, Muller et al have proposed a pathomechanism for lesion production which includes: "(1) the binding of pemphigus antibody at the glycocalyx of keratinocytes, (2) internalization of the pemphigus antibody and fusion of the antibody with intracellular lysosomes, and (3) resultant activation and release of a keratinocyte proteolytic enzyme ("pemphigus acantholytic factor"), which diffuses into extracellular space and hydrolyzes the glycocalyx" resulting in "acantholysis and blister formation within the epidermis."² The acantholysis in pemphigus has been likened to a Type II hypersensitivity reaction. There seems to be a controversy remaining over whether or not complement is involved in lesion production in pemphigus. Muller et al² believe that "pemphigus antibody-induced acantholysis is not dependent on complement or inflammatory cells." However, Jordan et al state that "complement activation by pemphigus antibodies provides an additional mechanism for loss of epidermal cell cohesion in addition to the plasminogen-plasmin system."³ It has long been known that complement (especially C3) deposits are present in pemphigus lesions as has been shown through immunofluorescence staining, but their role in lesion produc-

*Dr. Takayama is a 1990 graduate of the College of Veterinary Medicine.

**Dr. Busch, formerly a resident in Internal Medicine in the College of Veterinary Medicine at Iowa State University, is in private practice in Baltimore, Maryland.

lesion production is still not clear. Medleau et al seemed to clear up the discrepancy best. She states that "complement does not appear to have a primary role (in lesion production) because IgG from C3-depleted serum can induce acantholysis in epidermal cell cultures, however, complement may have a secondary role in that extracellular proteases released subsequent to pemphigus binding may generate chemotactic fragments of C3 or C5 which in turn could recruit polymorphonuclear granulocytes into the area."⁴

Pemphigus Vulgaris

Of the pemphigus complex, pemphigus vulgaris was first reported in 1975 and has been recognized in dogs and cats. The disease does not seem to have any age, breed, or sex predilections. It is a vesiculobullous disease that quickly develops into erosive/ulcerative lesions of the skin, oral cavity, and mucocutaneous junctions. Muller et al² report that "ninety percent of dogs and cats with pemphigus vulgaris have oral lesions." Pemphigus vulgaris lesions, strictly limited to the skin, are rare.⁷ In dogs, the cutaneous lesions are commonly found in the axillary and groin areas. Although this is a vesiculobullous disorder, vesicles are very transient and fragile, thus the clinical lesions appear as erosions and ulcers bordered by epidermal collarettes.^{2,6} The Nikolsky sign is characteristic of pemphigus and can be elicited by applying finger pressure at the lateral aspect of an erosion or to normal-appearing skin, which would dislodge the epidermis from the dermis thus creating a new erosion. This sign may or may not be present and is not diagnostic for pemphigus. The disease may also have systemic effects in which anorexia, depression, and fever may be present. In the dog, the list of differential diagnoses for pemphigus vulgaris include: bullous pemphigoid, systemic lupus erythematosus, erythema multiforme, toxic epidermal necrolysis, drug eruption, mycosis fungoides, lymphoreticular neoplasia, candidiasis, and numerous causes of ulcerative stomatitis.²

In the cat, lesions of pemphigus vulgaris commonly affect the gums, lips, hard palate, and nasal philtrum.⁶ Vesicles and bullae are rarely seen, thus erosions and ulcers are the usual clinical presentations. The list of differential diagnoses for ulcerative stomatitis in the cat is quite extensive. According to Manning et al⁸ the differentials include: recurrent necrotizing stomatitis, Vincent's stomatitis, renal disease, vitamin defi-

ciency, diabetes, heavy metal poisonings, viral diseases (FeLV, feline rhinotracheitis, feline calicivirus), neoplasia, granuloma, pemphigus, and lupus erythematosus.

Pemphigus Vegetans

Pemphigus vegetans is believed to be a benign variant of pemphigus vulgaris and has been rarely reported in the dog.^{2,9} In humans, pemphigus vegetans is classified as either the Neumann or the Hallopeau type. Clinically, the Neumann type forms vesicles and bullae as in pemphigus vulgaris, but during the healing process the affected areas form verrucous vegetations. The Hallopeau type form pustules initially and also have a papillomatous, proliferative healing response.⁹ There are apparently no age, breed, or sex predilections. Differentials for pemphigus vegetans include: bacterial and fungal granulomas, lymphoreticular neoplasia, mastocytoma, papilloma and fibropapilloma.²

Pemphigus Foliaceus

Pemphigus foliaceus is considered the most common form of pemphigus in the dog and cat. There seems to be no sex predilection. The disease seems to affect middle-aged dogs and according to a study done by Ihrke et al, four breeds of dogs were at a higher risk: Bearded Collie, Akita, Newfoundland, and Schipperke.¹⁰ Muller² adds Chow Chows, Doberman Pinschers, and Dachshunds to the above list of breeds that are apparently predisposed to pemphigus foliaceus. They often have footpad lesions characterized by erythematous swelling at the pad margins, cracking, and villous hypertrophy (villous hyperkeratosis or "hard pad").^{2,10} These footpad lesions often cause pain with resulting lameness. Vesicles and bullae are transient and the animals are usually presented with pustules and erosions bordered by epidermal collarettes. The epidermal collarettes with accompanying alopecia, scaling, and crusting usually start on the face, bridge of the nose, and pinnae then gradually spread to the ventrum. As with the other variants of pemphigus (i.e. -- pemphigus vulgaris), pain and pruritus are variable and anorexia, depression, and fever are seen in severely affected animals.²

Scaling and crusting are the most common clinical signs in cases of pemphigus foliaceus hence the origin of the name, "foliaceus", meaning leafy.¹⁰ Noxon and Myers reported a case of

pemphigus foliaceus in two Shetland Sheepdog littermates. They stated that although "pemphigus foliaceus generally is not regarded as an autoimmune disease with strong genetic influence" they did find two littermates from a litter of five that were diagnosed as having pemphigus foliaceus. They went on to state that "familial occurrence of pemphigus foliaceus has been reported in humans and that development of many autoimmune diseases is determined to a great extent by inheritance."¹¹

In the cat, pemphigus foliaceus is similar to what was described above for the dog. It is characterized by facial exfoliative dermatitis around the nose, periorbital area, and the pinnae.⁸ As with the dog, oral lesions are rare. More commonly seen are crusts, scales, alopecia, erosions, and epidermal collarettes. Footpad lesions can also occur.

Differentials for facial dermatitis in the cat are quite extensive: bacterial folliculitis-furunculosis, fungal dermatitis, demodecosis, allergic dermatitis (food), solar dermatitis, squamous cell carcinoma (white areas), seborrhea, pemphigus, systemic lupus erythematosus, notoedric mange, sarcoptic mange, otodectic mange, and drug eruption.⁸ In dogs the differential list is similar: bacterial folliculitis, dermatophytosis, demodecosis, dermatophilosis, seborrhea, lupus erythematosus, subcorneal pustular dermatosis, sterile eosinophilic pustulosis, linear IgA dermatosis, zinc-responsive dermatitis, dermatomyositis, and lymphoreticular neoplasia.²

Pemphigus Erythematosus

Pemphigus erythematosus, is thought to be a benign form of pemphigus foliaceus. No age or sex predilections are apparent, but Muller et al² states that in dogs, Collies and German Shepards may be predisposed to the disease. Lesions are similar to that of pemphigus foliaceus, however, the lesions are restricted to the face and ears. Depigmentation of the nose is often a complication, thus allowing photodermatitis to be a possible sequela.² Differentials are the same as for pemphigus foliaceus.

Diagnosis

Definitive diagnosis of pemphigus requires a good history and physical examination, followed by direct smears, and histopathologic examination with immunofluorescence or immunoperoxidase

testing.^{2,6} It is recommended that histopathology together with immunopathologic evaluations be used as the diagnostic approach to autoimmune skin diseases.^{4,12} Routine blood work (hemogram, serum chemistries) are usually non-specific in the cases of pemphigus vulgaris and pemphigus foliaceus. Results usually reveal a mild-to-moderate nonregenerative anemia, mild hypoalbuminemia, mild-to-moderate increases in globulins, and with pemphigus foliaceus, a slight eosinophilia.²

Direct smears should be done on intact vesicles or pustules. The smears can be stained with a variety of preparations including Wright's stain, new methylene blue, Quick stain, Sedi stain, and Papanicolaou's stain.¹² Microscopic examination will reveal large numbers of neutrophils and/or eosinophils, few bacteria, and acantholytic keratinocytes. The acantholytic cells are highly suggestive of pemphigus but do not in themselves offer a definitive diagnosis of pemphigus.

Skin biopsies must be done on intact vesicles, which may pose a problem in that these vesicles are very transient and fragile. Multiple sites may need to be biopsied to reveal pathologic changes indicative of pemphigus. Muller et al² recommends hospitalizing the animal in order to check its skin every 2 to 4 hours for blisters. They also go on to state that these "blisters rapidly fill with leukocytes and grossly and microscopically appear as pustules which could confuse both the clinician and the pathologist."²

Histopathologically, "pemphigus vulgaris is characterized by suprabasilar acantholysis with resultant cleft and vesicle formation." Single epidermal cells remain attached along the underlying basement membrane and resemble "a row of tombstones."^{2,7} In the cat, classical histopathologic changes are seldom seen, thus the diagnosis of pemphigus vulgaris may need to be based on only direct smears and direct immunofluorescence testing.⁸ Pemphigus vegetans is characterized histologically by acantholysis, papillomatosis, and intraepidermal microabscesses containing acantholytic keratinocytes, eosinophils, and/or neutrophils.^{2,12} Pemphigus foliaceus and pemphigus erythematosus appear histologically similar. They are characterized by intragranular or subcorneal cleft and vesicle formation and contain neutrophils or eosinophils along with acantholytic keratinocytes. Cells from the stratum granulosum are often found attached to the overlying stratum corneum within the vesicle and are termed granular cell "cling-ons."² Cats with pemphigus foliaceus and pemphigus erythema-

tosus have similar histopathologic changes characterized by subcorneal blisters and acantholysis.⁸

Muller et al² also lists histologic findings that may aid in the diagnosis of pemphigus in dogs and cats: "(1) a lichenoid cellular infiltrate (mononuclear cells, plasma cells, neutrophils, (2) eosinophilic exocytosis and microabscess formation within the epidermis or follicular outer root sheath (pemphigus foliaceus, erythematosus, vegetans), (3) involvement of the follicular outer root sheath in the suprabasilar, intraepidermal, intragranular, or subcorneal acantholytic process, and (4) acantholytic, dyskeratotic granular epidermal cells ("grains") at the surface of erosions (pemphigus foliaceus and erythematosus).²

Immunofluorescence or immunoperoxidase testing are needed for the definitive diagnosis of pemphigus after all of the above diagnostic "push-ups" are performed. Direct immunofluorescence testing seems to be favored over indirect immunofluorescence due to the high number of negative results with the indirect method. It is imperative that lesional (intact blisters or pustules) as well as perilesional skin be biopsied.^{2,6} The presence of immunoglobulin (usually IgG) and occasionally complement deposition in the intercellular substance helps support a definitive diagnosis of pemphigus.

Therapy

Therapy of pemphigus is usually based on the premise of controlling or managing the clinical manifestations of the disease. This is due to the fact that medical treatment must be continued for long periods of time, and often for the life of the animal. The goal of therapy is immunosuppression to negatively control or regulate immunologic reactivity. The immunosuppressive agents commonly used in the clinical management of pemphigus include the corticosteroids alone or in conjunction with cytotoxic or immunomodulating agents.

The most widely used glucocorticoid for the initial treatment of pemphigus is prednisolone or prednisone. Prednisolone must be given in immunosuppressive doses which range from 2.2 to 4.4 mg/kg orally each day for dogs. Cats need a higher dose which ranges from 4.4 to 6.6 mg/kg given orally each day.^{2,6} The dose can be divided into two treatments, thus stressing that therapy must be individualized in order to minimize adverse side effects (to be discussed below). The

above recommended dose for initial treatment of pemphigus has been recognized to control only about 50% of the cases in terms of remission of clinical signs.^{2,14} In a study done by Scott et al, a larger dose of prednisolone was used (6.6 mg/kg/day) in 31 dogs and proved efficacious in 94% in terms of inducing a remission of primary skin lesions, however, glucocorticoid side effects were greatly increased.¹⁵ Cats seem to respond well to glucocorticoid treatment alone and upon resolution of primary lesions, cats, as well as dogs, can be placed on alternate day/night maintenance prednisolone therapy to maintain remission.⁸

An alternative method of corticosteroid treatment in the dog, corticosteroid pulse therapy, involves the parenteral administration of methylprednisolone sodium succinate (11 mg/kg IV over 1 hour for 3 consecutive days).^{2,16} This treatment regime was adapted from human medical therapy for autoimmune skin diseases. According to White et al¹⁶, corticosteroid pulse therapy proved efficacious in rapidly resolving skin lesions in all the dogs in their study, and did not elicit any of the adverse side effects linked to high dose corticosteroid therapy.

Corticosteroids given at immunosuppressive levels have the following effects: "(1) decrease in circulating lymphocytes and monocytes, (2) decrease in certain lymphocyte and monocyte functional capabilities, and (3) decrease in immunoglobulin and complement levels."¹⁷ Major side effects in the study done by Scott et al¹⁵ included polydipsia, polyuria, polyphagia, lethargy, depression, muscle wasting, hepatopathy, and pancreatitis in addition to infection (especially in the urinary tract), thromboembolism, gastrointestinal hemorrhage, osteoporosis, and cushingoid signs and symptoms. Gastrointestinal side effects, such as indigestion and ulceration, caused by high doses of corticosteroids can be controlled by including cimetidine in the treatment protocol. Although thorough research has not fully documented the use of cimetidine to control gastrointestinal side effects, its inclusion in the treatment protocols has been clinically efficacious.

Because of the above-mentioned side effects with the use of high doses of corticosteroids, chemotherapy can be used in conjunction with prednisolone. This combination will not only help minimize side effects due to the prednisolone by lowering its dose requirements, but will aid in the treatment of pemphigus if corticosteroids alone cannot induce remission of the disease. Ihrke et al recommends instituting combination therapy if

the animal has not shown substantial improvement within 10 days after corticosteroid therapy was initiated or if the maintenance dosages (less than or equal to 1.1 mg/kg on alternate days) cannot be achieved within 3 to 4 weeks.¹⁰

Cytotoxic agents and immunomodulating drugs used include: azathioprine, chlorambucil, cyclophosphamide, cyclosporine, aurothioglucose, and dapsone.^{2,10,14,15} Dapsone has not been approved for use in dogs and cats in the United States and was not found efficacious in the study done by Scott et al.¹⁵ Muller cautions the use of azathioprine in cats due to their susceptibility to azathioprine toxicity.²

Although chemotherapy and chrysotherapy will lower the required dosage of corticosteroids, these drugs are not without adverse side effects or toxicities. Of the numerous side effects possible, depending on the drug chosen, of most importance is myelosuppression which is a common feature of all of the above-mentioned cytotoxic or immunomodulating drugs. Thus, monitoring the patient with a hemogram at least once a month will aid in individualizing a suitable treatment regime. Drug dosages should be adjusted to maintain a leukocyte count of no lower than 3000 per mm³ to minimize risk of infection. Although chrysotherapy has been used successfully in several studies^{10,14,15} it is usually not the drug of first choice in the clinical management of pemphigus. Patients are usually started on corticosteroids initially, and possibly combination therapy with azathioprine or cyclophosphamide later.^{2,10}

The prognosis for an animal diagnosed as having pemphigus must be guarded due to the possibility of life-long treatment and periodic monitoring regardless of the treatment regime instituted. The study of pemphigus complex in dogs and cats has brought many insights into the diagnosis and treatment of the autoimmune disorder in both animals and humans.

References

1. Sams WM Jr., Gammon WR. Mechanism of lesion production in pemphigus and pemphigoid. *J Am Acad Derm.* 6:431-449. 1982.
2. Muller GH, Kirk RW, Scott DW. Immunologic diseases. In: *Small Animal Dermatology*, Philadelphia: WB Saunders Co. 150-243, 427-574. 1989.
3. Jordan RE, Kawana S, Fritz KA. Immunopathologic mechanisms in pemphigus and bullous pemphigoid. *J Invest Derm.* 85: 72-76. 1985.
4. Medleau L, Dawe DL, Scott DW. Complement immunofluorescence in sera of dogs with pemphigus foliaceus. *Am J Vet Res.* 48:486-487. 1987.
5. Gorman NT, Werner LL. Immune mediated diseases of the dog and cat. I. Basic Concepts and the systemic immune-medicated diseases. *Br Vet J.* 142:395-398. 1986.
6. Scott DW. Pemphigus in domestic animals. *Clin Derm.* 1: 141-152. 1983.
7. Scott DW, Manning TO, Smith CA, Lewis RM. Pemphigus vulgaris without mucosal or mucocutaneous involvement in two dogs. *JAAHA.* 401-404. 1982.
8. Manning TO, Scott DW, Smith CA, Lewis RM. Pemphigus diseases in the feline: seven case reports and discussion. *JAAHA.* 18:433-443. 1982.
9. Schultz KT, Goldschmidt M. Pemphigus vegetans in a dog: a case report. *JAAHA.* 16: 579-582. 1980.
10. Ihrke PJ, Stannard AA, Ardans AA, Griffith CE. Pemphigus foliaceus in dogs: A review of 37 cases. *JAVMA.* 186: 59-69. 1985.
11. Noxon JO, Myers RK. Pemphigus foliaceus in two Shetland Sheepdog littermates. *JAVMA.* 194:545-546. 1989.
12. Akerman LJ. Canine and feline pemphigus and pemphigoid. Part I. Pemphigus. *Compend Contin Educ Prac Vet.* 7:89-97. 1985.
13. Suter MM, Palma DG, Zindel S, Schenk H. Pemphigus in the dog: Comparison of immunofluorescence and immunoperoxidase methods to demonstrate intercellular immunoglobulins in the epidermis. *Am J Vet Res.* 45:367-369. 1984.
14. Ackerman L. Pemphigus and pemphigoid in dogs and cats. Part I: Clinical signs, diagnosis and treatment. *Mod Vet Prac.* March:260-265. 1986.

15. Scott DW, Manning TO, Smith CA, Lewis RM. Observations on the immunopathology and therapy of canine pemphigus and pemphigoid. *JAVMA*. 180: 48-52. 1982.

16. White SD, Stewart LJ, Bernstein M. Corticosteroid (methylprednisolone sodium succinate)

pulse therapy in five dogs with autoimmune skin disease. *JAVMA*. 191: 1121-1123. 1987.

17. Fauci AS. Clinical aspects of immunosuppression: Use of cytotoxic agents and corticosteroids. In: *Immunology III*, Bellanti JA, WB Saunders Co. 546-556. 1987.



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